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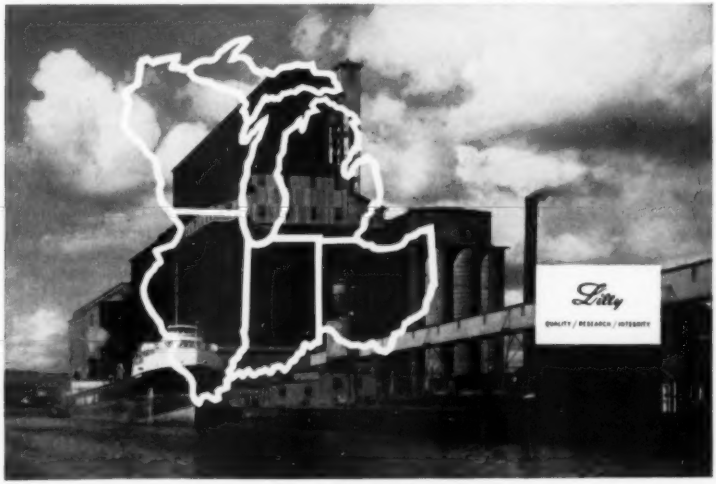

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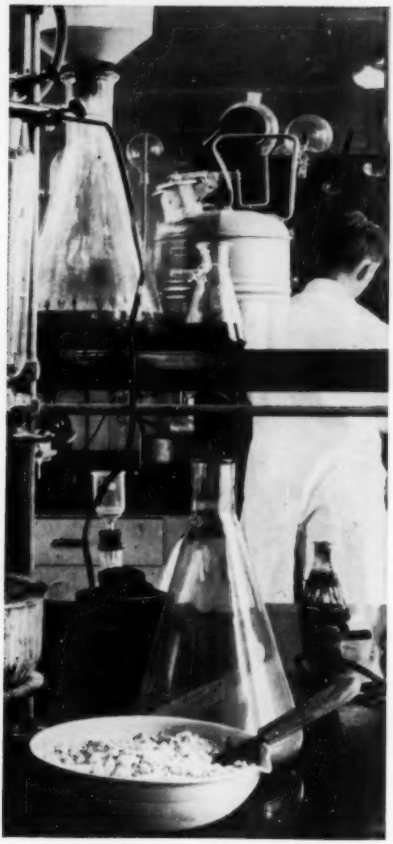

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OUR COVER

DR. IVOR GRIFFITH

ON October 8, 1959, Doctor Ivor Griffith announced his resignation as Dean of the faculty of the Philadelphia College of Pharmacy and Science. It is fitting at this time that we pen these words for the opening of the new college term marked the beginning of fifty years of uninterrupted service by Dr. Griffith to his Alma Mater as student, alumnus, president of the Alumni Association, instructor, professor, head of the Department of Pharmacy, Editor of the *American Journal of Pharmacy,* dean, and finally as the President of the College. He is the only man in the 138 year history of our College who has occupied all of these positions. His self-sacrificing labor for his Alma Mater and his constructive work still being carried on as President will be held in lasting remembrance.

Unassuming and unaffected, he remains today a vigorous personality, full of energy, ready in debate, wise in counsel, and of unfailing courtesy and good humor. As a teacher and educator, all appreciated him for the gift he has of imparting scientific knowledge simply, directly, and understandingly. As head of the academic group at the College, his stimulating influence has been far-reaching. He has done yeoman service in strengthening and directing the executive work of the College and establishing it on a firm foundation.

The life and career of Ivor Griffith has been active, productive, rich, and colorful. He has an independent, keen, versatile, and creative mind. Space does not permit enumeration of his many outstanding scientific contributions and the honors which have come to him. He is a man of many facets and the range of his interests is wide in scope. A staunch supporter of what he believes to be right, he is frank and outspoken and a courageous and resourceful adversary of what he considers unjust and wrong. Add to all of this his breadth and vision in civic life and we have in Ivor Griffith a superb symbol of the American way of life.

Ivor Griffith, an immigrant, self-made, who cut through all hazards of poverty, is the answer to those who forget or fail to recog-

nize that America is a beautiful symphony where each and every group, contributing its skill and genius, plays, and must play, in harmony and this very diversity of instrumentation gives the symphony its depth and profundity.

Many of the members of the present faculty have long had and will continue to have the privilege of working with him. All have enjoyed this association and have profited from his experience and counsel. In adding our tribute and recognition of his fifty years of successful and inspiring service, we pray that he be spared for many years. These we hope will be caravan laden with health, happiness, usefulness and contentment. May the lessons of his service, as it continues, be a heritage to all workers whose value time cannot obscure and emulation can but enhance.

Louis Gershenfeld,
Chairman,
Faculty Council,
Philadelphia College of Pharmacy and Science

E D I T O R I A L

FOR BETTER CONTROL IN THE DISTRIBUTION OF DRUGS

A considerable amount of criticism, much of it justified, has been forthcoming in recent months with respect to the improper distribution of dangerous drugs. Here, we are speaking not of the controversy concerning OTC drugs and proprietary preparations packaged and labelled for direct sale to the ultimate consumer but rather of bona fide prescription drugs which are supposed to be dispensed *only* on the prescription of a licensed physician. Only too often, the practicing pharmacist is considered as the only one responsible for the improper distribution of such drugs and for the fact that they do get into lay hands in rather large amounts. The situation is particularly acute in the case of the central stimulants and hypnotics and we suspect that the illicit commerce in these drugs has reached unbelievable proportions.

The real facts of the case show that there is far too much laxity involved in the distribution of drugs *before* they reach the custody of the practicing pharmacist. Whereas the Food, Drug, and Cosmetic Act and those responsible for its enforcement have exerted great pressure on the pharmacist to keep him from being an illicit source, little or no effort has been made at the manufacturing level and in the distribution to certain fly-by-night wholesalers and other distributors of questionable status and integrity.

It is not difficult for a layman to purchase prescription drugs outside legitimate distributive channels and without a physician's prescription if he really sets his mind to it. Some of the loopholes which need to be plugged are well-known but it will do no harm to list a few here. Some drug manufacturers feel that they are privileged to sell drugs to industrial plants even though such drugs are ordered by neither a physician nor a licensed pharmacist. Thus, for example, a purchasing agent can often buy prescription drugs by the simple expedient of ordering them. Often, it is claimed that these are for the

use of the industrial health department or the medical director but no check is made to determine if such is the case. A registered nurse—although she has no legal authorization to do so—can often purchase prescription drugs and, here again, it is assumed that she is buying them for the use of some physician with whom she works or by whom she is employed. Persons engaged in research, even though they are neither pharmacists or physicians, usually have their purchase order for drugs honored even though such drugs may not be intended for laboratory or animal experiment but rather for themselves, their friends, or their families. Many so-called wholesale drug establishments do not have a single professionally qualified person in the organization and, yet, these establishments have their orders honored by certain manufacturers. Another very important source of improper distribution lies in the detail men representing certain pharmaceutical companies. Many of these representatives are not pharmacists and, even though they may be considered as legal agents of the manufacturer, there is some question in our mind concerning the propriety of entrusting dangerous drugs to such persons since it is obviously impossible to determine whether they are properly or improperly disposed of.

The physician's sample frequently is found in unauthorized hands and the process by which it gets there is quite varied. Frequently it has never been delivered to a physician in person but has been handed out by a company representative, the physician's secretary, or some other office employee. Even cleaning women and janitors—who these days are pretty well-informed—know which samples which they see lying about represent a drug which they themselves or a friend might wish to use.

The time has come when the entire chain of drug distribution should be more carefully controlled and restricted to those professionally trained persons who both know what they are doing and are legally responsible for their acts. We surely do not condone the over-the-counter sale of prescription drugs by the retail pharmacist and we know better than to justify such an evil by citing a similar evil but it is still worse for such prescription drugs to be sold or given away by those who have no professional knowledge at all. We predict that, unless manufacturers have wholesalers institute some rather rigid controls and do so without delay, they will soon become restricted by federal legislation just as is the retail pharmacist. It is not asking

too much to expect those who manufacture and distribute drugs to make certain that prescription drugs are sold only to those persons who are privileged under the law to dispense or use them. It is true that proper controls may to some extent dry up certain sales outlets but these should not have existed in the first place. It will not cause any loss in total sales but only a readjustment of the avenues through which the sales are made. Prescription drugs either require professional supervision or they do not. It is illogical to rigidly control one group of persons through whom they may be distributed improperly and then allow others to do with them exactly as they please.

L. F. Tice

APPROACHES TO THE TREATMENT OF ATHEROSCLEROSIS

By Thomas H. F. Smith *

IN the event that medical research scientists, clinicians, and the general public of the United States were asked to select the most important disease process against which humanity must struggle for existence, the results might be expected to approach a close tie between cancer and atherosclerosis. When we consider that the atherosclerotic process is manifest in the coronary arteries of the majority of American males more than 25 years of age, and that approximately one-third of all deaths among male Americans age 45-54 may be attributed to arteriosclerotic and degenerative heart disease (1), the epidemic proportions of this condition become evident. Almost without reservation, atherosclerosis can be designated the "number one killer," not only of the elderly but of the middle-aged American male in the prime of life (1).

This review is devoted to a consideration of certain concepts which form the rationale for pharmaceutical products currently in use for the prophylaxis or therapy of the atherosclerotic condition. Each topic is followed by examples of marketed products relating to that particular section. No attempt has been made to provide a complete listing of the commercial products available in each category; therefore, the inclusion or omission of a specific product should not be considered an indication of relative merit or preference. Within each class, the products are arranged alphabetically by proprietary names, and the amount of the active ingredient in a therapeutic dose is shown for comparison purposes. In most cases, a product is considered in only a single category, although it may contain more than one ingredient. Therapeutic agents recognized by the U. S. P. or N. F. are indicated as such without reference to proprietary names.

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General Concepts of the Etiology of Atherosclerosis

Since it is essentially a disease, atherosclerosis is neither inevitable nor irreversible. It should rather be considered preventable and, if discerned at an early stage, curable.

The multiple etiological factors leading to atherosclerosis are illustrated by Friedman *et al.* (2) by the following scheme:

$$\text{Time} \times \begin{matrix}\text{Intrinsic}\\ \text{Intimal}\\ \text{Derangement}\end{matrix} \times \begin{matrix}\text{Quantitative and}\\ \text{Qualitative Alter-}\\ \text{ation of Plasma}\\ \text{Lipids and Choles-}\\ \text{terol}\end{matrix} \times \begin{matrix}\text{Blood}\\ \text{Pressure}\end{matrix} = \begin{matrix}\text{Athero-}\\ \text{sclerosis}\end{matrix}$$

From this equation, it would appear that all interacting conditions are included and that varying degrees of emphasis may be placed on any given factor without disturbing the basic integrity of the equation.

An incorrect concept of "Time" in this formula must not be formed. "Time" is interpreted here as the duration of certain modifications, rather than the aging process. As expressed by Aschoff (3), "If arteriosclerosis were merely a phenomenon of aging, neither remedies nor prophylaxis would avail, for no one can escape age and death." On the other hand, thinking in terms of "duration of modification," the many reported experimental animal studies all indicate the need for certain alterations of diet or some other variable for *extended periods* of time. Atherosclerotic changes do not occur spontaneously but require "Time" to become manifest.

A new concept of the intrinsic intimal derangement problem has been recently published by Page (4). Previously neglected components of connective tissue and the significance of the naturally occurring balance between fibrin and fibrinolysin, with respect to atherogenesis, are emphasized. Tunbridge (5) reported on an earlier consideration of connective tissue, and a Ciba Foundation Symposium (6) elaborated the chemistry and biology of the mucopolysaccharides.

The lipids and their role in the atherosclerotic process are presented in detail by Page (7). The biochemistry and pathological significance of cholesterol has been presented by both Kritchevsky (8) and Cook (9).

The final component of Friedman's formula is blood pressure. Atherosclerosis is a process separate and different from—but intertwined with—hypertension (1). That atherosclerosis can occur in the

absence of hypertension has been frequently demonstrated, but that they often occur together has also been established. In the final analysis, the evidence concerning the interrelationship of these two conditions indicates that, like "yin" and "yang" in the ancient Chinese symbol of the cosmos, they complement one another, one following the other in a vicious circle that ends at the grave. An unbiased review of this aspect of the subject is presented by Schroeder (10), and the historical background of this problem is described in a review by Cowdry (11).

Public interest and feverish scientific activity have stimulated members of many related disciplines to explore the atherosclerosis problem within the scope of their particular field. These fresh approaches have suggested, among other things, that modifications of hormonal and nutritional factors may be implicated in this process (12, 13). The work of Katz, Stamler, and Pick (1) indicates the importance of dietary factors in the etiology of atherosclerosis. The value of dietary modifications in preventing and promoting the regression of the atherosclerotic condition in man and animals has been examined by many investigators.

An analysis of the relationship of certain foods and the incidence of atherosclerosis has offered a positive correlation and suggested that dietary modifications might combat this situation effectively. For many reasons, this therapeutic measure has not materialized successfully for, as Page (14) has stated, "Something cannot be taken away from the American public without giving it something in return which it likes as well." It is difficult for the average person to accept a therapeutic regimen which produces no readily discernable alterations in his condition, in spite of prolonged treatment. The complication which presents itself in the prophylaxis of atherosclerosis is the innate reluctance of people to accept medicine when they do not feel "sick." Serum cholesterol levels and atherogenic processes are terms which the public has difficulty in appreciating in terms of the layman's concept of "disease." The increasing awareness of the public to atherosclerosis and its concurrent dangers will no doubt lessen the task of the physician. To assist him in his efforts, the pharmaceutical manufacturers have provided practically every substance which has been shown to be of therapeutic value in hypercholesterolemia and the atherosclerotic state.

The following portions of this review are concerned with the major pathological factors which influence atherosclerosis and the therapeutic agents which are available to combat these influences.

Cholesterol

Animal experiments have consistently demonstrated during the past half century that dietary cholesterol is one of the most important factors which influence total serum cholesterol concentrations (15). However, attempts to correlate clinical data on elevated serum cholesterol levels with the development of the atherosclerotic condition have not proven particularly successful. In the light of information available today, it is obvious that many factors are involved in addition to cholesterol. It should further be stated that agreement on the hypothesis, "In all cases of atherosclerosis, hypercholesterolemia is found," in no way precludes agreement on the inversion of the premise, "In all cases of hypercholesterolemia, atherosclerosis is found." It is an accepted fact that, in spite of consistent hypercholesterolemia in disease states such as diabetes, nephrosis, hypothyroidism, biliary obstruction, essential hypercholesterolemia, hyperadrenalcorticism, and adrenal insufficiency, atherosclerosis is not uniformly present (1). These observations indicate the caution which must be exerted in scientific thinking to prevent a confusion of cause and effect.

The A. M. A. council on Foods and Nutrition recently solicited comments from selected researchers in the field of atherosclerosis on the significance of elevated cholesterol levels in the etiology of atherosclerosis and the importance they placed also on the reduction of the serum concentration of this sterol as a therapeutic measure. In his reply, Hartroft (16) took a strong stand against attempts to lower elevated serum cholesterol levels and directed attention to other lipid abnormalities. By contrast, Ahrens and his associates (17) reported on the benefits to be derived from lowering elevated serum cholesterol levels. Ahrens suggests that since ". . . it has not been proven that the lowering of serum cholesterol will prevent the occurrence or the end results of atherosclerosis," it is justifiable to employ procedures which are "theoretically harmless and possibly beneficial."

The lowering of elevated serum cholesterol, whether advantageous or not, has been accomplished in many ways. Some of these methods will be considered here.

Agents Which Lower Elevated Serum Cholesterol Levels

Unsaturated Fatty Acids.—Ahrens (18) has reviewed the relationship of dietary fats to serum cholesterol levels in man. The accusing finger has been pointed at the saturated fatty acid components of natural fats, particularly animal fat, as being the major cause of elevated serum cholesterol levels. Since the average American normally consumes a diet rich in these saturated fatty acids during most of his life span, it was postulated that the replacement of these materials by unsaturated fatty acids should prove beneficial.

The ability of the unsaturated fatty acids to lower elevated serum cholesterol levels has been demonstrated repeatedly in both animal and human studies.

Katz *et al.* (1) suggest that a substitution rather than a simple supplementation of the diet with unsaturated fatty acids is necessary to obtain the maximum therapeutic effectiveness with these agents. This is in agreement with Keys (19) who feels that serum cholesterol levels are directly related to the total consumption of fat; therefore, effective correction of this situation involves a decrease in the concentration of saturated fats in the diet and their replacement with polyethenoid fatty acids. As yet, no long-term reports of the prophylactic or therapeutic use of unsaturated fatty acids in atherosclerosis are available (1). A recent article by Weiss (20) is devoted to the pros and cons of the unsaturated fatty acid-serum cholesterol problem.

The mode of action of the unsaturated fatty acids has not been conclusively resolved. Byers and Friedman (21) discount the possibility of decreased intestinal absorption of cholesterol resulting from the presence of these agents in the intestinal tract and rather propose that cholesterol absorption is enhanced by unsaturated fatty acids. Hirsch (22) offers the intriguing possibility that unsaturated fatty acids esterify with cholesterol and, in so doing, form a liquid ester of the otherwise high melting point sterol. This liquid ester tends to remain in solution in the body, unlike the insoluble complex which results from a combination of saturated fatty acid and cholesterol.

Another type of plant lipid, lecithin, has been considered to be of possible value in hypercholesterolemia. The term "lecithin" refers to a group of phospholipids consisting basically of the glycerophosphoric acid esters of fatty acids combined with choline. Lecithin has been used for many years as an emulsifying agent. The precise role of lecithin in human biochemical processes is not fully understood but

its importance appears indicated by its wide distribution in the body.

Experimental animal studies (23-25) revealed that a disproportionate increase in serum cholesterol levels could be reversed by dietary supplementation with phosphatides. Investigations of the value of lecithin in human atherosclerosis are presently being conducted, as well as studies on other phosphatide substances related to lecithin which may also prove of therapeutic value.

Some examples of available products in this class are shown in Table I. The first section lists products containing unsaturated fatty acids of plant origin, principally linoleic acid. The second group consists primarily of products containing lecithin derived from soy beans.

TABLE I

PRODUCTS CONTAINING UNSATURATED FATTY ACIDS OR GLYCEROPHOSPHORIC ACID ESTERS OF UNSATURATED FATTY ACIDS OF PLANT ORIGIN

A. Unsaturated Fatty Acids

Product	*(Manufacturer)*	*Linoleic Acid content/dose*
Liquids		
ARCOFAC	(Armour)	6.0 Gm./15 cc.
ATHEROXIN	(Harvey)	4.2 Gm./15 cc.
LINODOXINE	(Pfizer)	4.5 Gm./15 cc.
SAFF	(Abbott)	7.0 Gm./15 cc.
SAFFLEX	(L. D. W.)	6.5 Gm./15 cc.
Capsules		
ALESTROL	(Testegar)	530 mg./capsule
LENIC	(Crookes-Barnes)*	495 mg./capsule*
LUFA	(U. S. V. C.)	294 mg./capsule
SAFFOLIN	(Tutag)	370 mg./capsule

* LENIC CAPSULES (Crookes-Barnes) contain also oleic acid—175 mg.; linolenic acid—20 mg.; and tetraenoic, hexaenoic, and pentaenoic acids—100 mg. (total of the three). This represents 880 mg. UFA/capsule.

B. Glycerophosphoric Acid Esters of Unsaturated Fatty Acids

Product	*(Manufacturer)*	*Lecithin content/dose*
	Liquid	
E. F. A.	(Columbus)	300 mg./15 cc.
	Granules	
R. G. Lecithin	(Central Soya)	2.8 Gm./15 cc.

There are several synthetic products worthy of consideration which contain unsaturated fatty acids but have been designed for use as foods rather than as medicines. Two powdered milk-type preparations, free of butter fat and consisting essentially of plant fats in a dry form, are LONOLAC (Mead Johnson) and SAFLAC (Carnation Milk). Pitman-Moore offers EMDEE MARGARINE for those who must restrict the consumption of butter in the diet. This spread contains 80% corn oil or, by conversion, 45.6% linoleic acid.

Although the therapeutic value of the unsaturated fatty acids in atherosclerotic conditions continues to be debated and much information is lacking in regard to their mode of action, they continue to remain in use.

Phytosterols.—In 1951, Peterson (*26*) was the first to demonstrate that sitosterol, a member of a group of plant sterols known as phytosterols, would prevent the development of hypercholesterolemia in cholesterol fed chicks. In a later study, Peterson (*27*) showed that the administration of sitosterol reduced the incidence of aortic atheromatous lesions which develop in untreated chicks fed a high cholesterol diet. Pollack (*28*) substantiated the hypocholesterolemic action of sitosterol in humans having elevated serum cholesterol levels prior to treatment with this agent. Shipley and others (*29*) report that beta-sitosterols have been administered to humans for periods exceeding four years without any apparent adverse effects being observed. They also found no evidence of toxicity in rats, rabbits, and dogs given large daily doses (4 Gm./day) of beta-sitosterols for periods up to two years.

The hypocholesterolemic action of sitosterol as explained by Davis (*30*) is due to the formation of a mixed crystal of sitosterol and

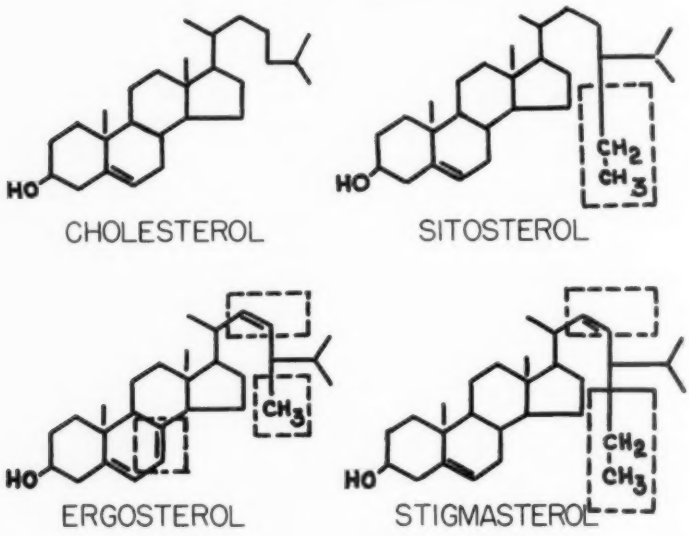
cholesterol which is less soluble than cholesterol itself. In this combination, cholesterol is largely unavailable for absorption into the circulation. The exact mechanism of the apparent inhibition of cholesterol absorption by sitosterols remains to be elucidated.

Only one product is marketed containing sitosterols. This is a mixture of beta- and dihydro-beta- sitosterols (20% emulsion) available as CYTELLIN (Lilly).

The investigations of the sitosterols renewed interest in other closely related plant sterols. Among the various plant sterols which were examined and compared to sitosterol for their ability to reduce serum cholesterol levels were ergosterol and stigmasterol. A comparison of the structural formulas of these compounds is shown in Figure 1.

FIGURE 1.

A COMPARISON OF THE STRUCTURAL FORMULAS OF CHOLESTEROL, SITOSTEROL, ERGOSTEROL, AND STIGMASTEROL.



The examination of these structures reveals that sitosterol differs from cholesterol only by the inclusion of an ethyl group on carbon 24. Ergosterol is found to contain three double bonds (2 in the

phenanthrene nucleus and 1 between carbon 22 and 23 in the carbon 17 side chain) in contrast to cholesterol and sitosterol which have only one double bond in the nucleus and none in the carbon 17 side chain. Stigmasterol is closely related to sitosterol, having a similar ethyl substitution on the carbon 24 but differing by the presence of a double bond between carbon 22 and 23.

Peterson and others (31) reported in 1953 that ergosterol and stigmasterol were effective inhibitors of the progressive rise of plasma cholesterol in chicks fed an atherogenic diet.

Daskalakis and Chaikoff (32), working with rats, showed that ergosterol blocked the absorption of cholesterol to the extent of 50 per cent. In this same study, it was found that dihydroergosterol blocked cholesterol absorption to an extent of 80 per cent of control values whereas stigmasterol was ineffective in blocking cholesterol absorption.

Vitamins.—In the course of a continuing search for a safe and effective method for the correction of lipid abnormalities in man, Altschul and his colleagues (33) examined nicotinic acid. They found that oral administration of 1 to 4 grams of nicotinic acid in a 24 hour period reduced the level of serum cholesterol in both normo- and hypercholesterolemic patients.

These findings led Parsons and Flinn (34) to study the long-term effects of large doses of nicotinic acid in hypercholesterolemic patients. The results of these studies conducted over a three-year period (35) showed that the daily administration of 3 to 6 grams of nicotinic acid was an effective method for reducing serum cholesterol levels. They reported some objectionable side effects from the large doses of nicotinic acid. These did not prove serious but included: flushing, gastrointestinal distress, pruritis, and nervousness. These findings have been confirmed by Belle and Halpern (36) and Miller *et al.* (37). O'Reilly and his group (38) at Saskatchewan state that a sustained-release nicotinic acid preparation (NICOSPAN, Merrell—containing 500 mg. of nicotinic acid/capsule) was twice as effective as nicotinic acid in a regular dosage form in reducing elevated serum cholesterol levels of twenty patients in their hospital. (This product is not yet available for general use in the United States). Duncan and Best (39) have shown that long-term administration of nicotinic acid at the 1% level in the diet significantly depressed elevated serum cholesterol levels in rats.

The mechanism by which nicotinic acid reduces serum cholesterol levels is only partially understood (40), but there is evidence that it alters the enzyme systems of the liver which are involved in the synthesis of cholesterol and its subsequent conversion to bile acid. Merrill (41) suggested that the position of nicotinic acid in the phosphopyridine nucleotides and their relation in turn to the oxidation of steroids may account for the hypocholesterolemic activity of this substance.

Investigations of nicotinamide showed that it was ineffective for use in the reduction of serum cholesterol levels (1).

Nicotinic acid is an official U. S. P. product and is marketed by a variety of manufacturers in different dosage forms. For this reason, no separate listing of nicotinic acid products is included.

Pyridoxine or Vitamin B_6 has long been established as a factor in normal nutrition. It is involved in the metabolism of nerve cells and in the synthesis of amino acids. It also influences hematopoiesis by an action on the porphyrin ring.

Vascular lesions in monkeys similar to those observed in human atherosclerosis (42) and arterial hypertension in rats (43) have both been produced as the result of pyridoxine deficient diets.

Based on this information, Schroeder (44) investigated more thoroughly the results of a B_6 deficiency in the human. He concluded from his studies that a conditioned pyridoxal deficiency might be a contributing factor to the development of atherosclerosis in man. Schroeder further proposed that, although pyridoxine is present in the normal diet and is synthesized by intestinal bacteria, these amounts may not be sufficient to meet the body's requirements. Hence, a marginal pyridoxine deficiency may develop and exist for varying periods of time. Transient episodes of suboptimal intake may pass unnoticed, but the repetition of this deficiency over the years permits the gradual development of atherosclerotic lesions in the arteries.

A lack of pyridoxine for protein metabolic systems may also interfere with fibril formation and allow an accumulation of undifferentiated ground substance in the arteries. Pyridoxine deficiency inhibits transamination and transsulfuration reactions essential to the formation of elastic tissue and collagen.

Sinclair (45) and Tulpule and Williams (46) studied the role of pyridoxine in the reaction which causes the conversion of linolate to

arachidonate. Other evidence indicates that it is involved in transamination and decarboxylation reactions in the body. These indications would appear to implicate pyridoxine in the utilization of unsaturated fatty acids, an important consideration in the problem of atherosclerosis.

Largely on the basis of such evidence, the prophylactic and therapeutic use of pyridoxine in atherosclerosic conditions has been advocated. Pyridoxine in capsular and injectable form is an official U. S. P. product. Many preparations which contain pyridoxine in combination with other ingredients are marketed for use in diversified conditions which are not relevant to this discussion; therefore, a list of these preparations is not included.

Myasnikow (47) observed that Vitamin C produced a striking hypocholesterolemic effect in rabbits, accompanied by a decrease in aortic atheromatous lesions. Anderson and Keys (48) attempted to confirm the hypocholesterolemic action of ascorbic acid in humans but were unable to reproduce the effects which Myasnikow obtained in the rabbit. The use of Vitamin C in atherosclerotic conditions is a popular form of therapy in the Soviet Union, the theory being that ascorbic acid increases the rate of oxidation of cholesterol and its subsequent elimination from the body.

With reference to Vitamin A, Weitzel (49) reported that the administration of Vitamin A to old hens effectively lowered serum cholesterol levels. Myasnikow (50) found no beneficial effect from the administration of Vitamin A, thiamin, or riboflavin.

Dam (51) observed that Vitamin E did not modify aortic cholesterol deposition in cholesterol-fed rabbits or chicks. Marx *et al.* (52) found that neither E avitaminosis nor a large intake of this vitamin modified either plasma or tissue cholesterol or the progression of the experimental atherosclerotic state in rats. Contrary to these findings, Morgulis and Spencer (53) claim that a significant rise in serum cholesterol occurs in rabbits fed a vitamin E deficient diet and Bruger (54) noted a marked increase in the aortic cholesterol content of rabbits fed tocopherol. These reports are fragmentary and species variations might account for the discrepancies which have been reported. This aspect of the over-all problem requires further exploration.

An investigation of pantothenic acid (55) revealed that it is intrinsically involved with the enzyme responsible for the activation of

acetate in the synthesis of cholesterol. A natural assumption followed that a deficiency of pantothenic acid might inhibit this reaction and thus result in a lowering of serum cholesterol levels. While this premise proved invalid, it did serve to open the gateway to investigations of co-enzyme A inhibitors and their effect on this metabolic pathway. (The co-enzyme A inhibitors are discussed in a subsequent section of this review.)

Lipotropic Agents.—Choline, inositol, and methionine have been investigated for possible hypocholesterolemic and anti-atherosclerotic activity. With few exceptions, the findings obtained have been negative (1). A dirth of information on long term studies prevents a definitive appraisal of their real value in the prophylaxis or treatment of atherosclerosis.

Choline, a component of lecithin, and methionine both serve as sources of labile methyl groups in certain transmethylation reactions, but little is known about the significance of this reaction in the atherosclerotic scheme.

Both positive and negative reports have appeared (1) concerning the value of inositol in the treatment of atherosclerotic disorders. However, it continues to be employed by some as a therapeutic agent in this condition.

Choline and inositol are official U. S. P. products and are manufactured as such by many companies. Combinations of choline, inositol, and methionine, often in combination with other additional ingredients, are offered in a variety of forms. Some examples are shown in TABLE II.

Inhibition of Cholesterol Synthesis.—A direct attack on the problem of reducing serum cholesterol levels would appear to be the inhibition of endogenous cholesterol synthesis.

Steinberg and Fredrickson (56) found that a significant reduction in the serum cholesterol level occurred in experimental animals upon administration of delta-4-cholestenone. It is believed that this sterol inhibits the biogenesis of cholesterol by interfering with the utilization of precursor substances. Careful clinical investigations (57, 58) have shown this compound is effective in reducing human hypercholesterolemia. Further studies revealed that a relatively high toxicity accompanied the chronic administration of this agent. Tompkins (59) pointed out that a steroid such as cholestenone, that results in high

TABLE II

LIPOTROPIC PREPARATIONS

Product	(*Manufacturers*)	*Choline*	*Inositol*	*Methionine*	*Content in mg.*
Parenterals					
AMVITOL	(Walker)	10	—	15	/cc.
METHISCHOL	(U. S. Vitamin)	100	15	25	/cc.
TROBEX	(Testegar)	50	—	25	/cc.
Liquids					
DELPHICOL	(Lederle)	1440	240	*	/15 cc.
GERICOLE	(Sherman)	750	300	—	/15 cc.
INCHOLIP	(Flint-Eaton)	3000	500	—	/15 cc.
LIPOTAINE	(Stuart)	210	—	—	/15 cc.
MONICHOL	(Ives Camerson)	1500	750	—	/15 cc.
WYCHOL	(Wyeth)	3000	450	—	/15 cc.
Capsules					
CHOLIMETH	(Central)	350	100	100	/capsule
DELPHICOLE	(Lederle)	350	38	190	/capsule
LIPOTROPIC	(Lakeside)	200	100	100	/capsule
METHISCHOL	(U. S. Vitamin)	277	83	111	/capsule
TYCOPAN	(Lilly)	53	53	—	/capsule

* Methionine as 1.22 Gm. acetyl-dl-methionine and 0.16 mg. folic acid.

tissue levels of cholestanol, could be expected to be atherogenic. These findings preclude the possibility of the therapeutic use of an agent of this type in atherosclerotic conditions.

Curran (60) found that vanadium salts in low concentrations had a marked effect on hepatic cholesterol synthesis *in vitro* and *in vivo* in the rat. A later study (61) of these salts showed that they significantly reduced aortic cholesterol deposition in rabbits when administered for a six-week period following four weeks of cholesterol feeding. Human investigations (62) of the diammonium oxytartrate salt of vanadium revealed its ability to greatly lower serum-free and total cholesterol and the cholesterol/phospholipid ratio in normocholesterolemic young men.

Garattini and his co-workers (63) formulated the concept that an interference of endogenous cholesterol synthesis could be elicited by the inhibition of co-enzyme A, which had previously been shown to be essential for the enzymatic conversion of acetate into cholesterol (55). Studies of phenylethylacetic acid and its analogs by Cottet *et al.* (64) showed these substances to be effective in blocking cholesterol synthesis *in vitro* and *in vivo*. These researchers recorded lowering of serum cholesterol by as much as 70-80 per cent of the pretreatment level with the use of phenylethylacetic acid in humans. Other investigators (65) were unable to elicit a similar effect on the circulating lipids with this agent.

Several encouraging reports appeared in a recent news release (66) concerning the investigations of a new synthetic compound, 1-[(4-diethyl-aminoethoxy)phenyl]-1-(p-tolyl)-2-(p-chlorophenyl) ethanol (MER-29, Merrell). The clinical information on the use of this compound reveals that the daily administration of 250 mg. of the drug reduced serum cholesterol levels from 325 mg.% prior to therapy to 48 mg. % after two weeks of treatment. No significant side effects occurred at this dose level but higher doses were accompanied by some nausea and vomiting. This agent is presently being further evaluated for the therapy of atherosclerosis and hypercholesterolemic conditions in humans.

Antibiotics.—Samuel and Steiner (67) found that neomycin (MYCIFRADIN, Upjohn), when administered to humans in an oral dose of 2 grams/day, reduced the pretreatment serum cholesterol levels of the patients studied an average of 22 per cent, for 3 to 16 weeks. They found that doses of 0.5 to 1 gram/day produced similar cholesterol lowering effects on the serum, but of a lesser degree.

Seaweed Derivative.—A sulfated polymannuronide, obtained from seaweed, effectively lowered the elevated serum cholesterol levels of hypercholesterolemic and hyperlipemic patients when administered intravenously in a dose of 10 mg./Kg., twice daily. Termination of therapy was marked by a return of the serum cholesterol to the previously elevated levels (68).

Marine Oils.—A number of investigators have demonstrated the fact that the isocaloric substitution of marine oils for saturated animal lipids in the diet will result in significant falls in plasma cholesterol levels (1). A recent report (69) claimed that oils obtained from

seals, sardines, and whales are effective in lowering elevated serum cholesterol levels in experimental animals.

Metal Salts.—Siperstein and others (70) observed that the feeding of ferric chloride to chickens being maintained on an atherogenic diet significantly lowered serum cholesterol levels in some cases. In a variation of the procedure, this salt prevented the rise of serum cholesterol which normally accompanies the feeding of an atherogenic diet to chicks. At autopsy, they found that the severity of atherosclerosis, as measured by aortic atheromatous lesions, was markedly less in ferric chloride-treated animals than in the untreated control group. These researchers postulate that possibly the ferric salt caused a binding of the bile in the intestine and thus prevented cholesterol absorption.

Brain Extract.—Jones (71) found that a crude residue of mammalian brain, remaining after serial extractions with acetone and then ether, depressed the serum cholesterol level and decreased the severity of aortic atherosclerotic lesions in chicks. Studies conducted in humans with a more purified product confirmed the results in the chickens with regard to the ability of this extract to lower serum cholesterol and lipids.

Chelating Agents.—Seven and Johnson (72) stated that it appears that the administration of EDTA (ethylene-diaminetetracetic acid) for prolonged periods may alter the extent of atherosclerotic plaques by removal of the calcium which forms the matrix for cholesterol deposition. Relatively few investigations offer clear-cut evidence about the influence of chelating agents on cholesterol metabolism and circulating cholesterol levels. This subject will require much additional exploration before the mechanisms of chelation in the atherosclerotic process are fully understood.

Miscellaneous Substances.—Newman *et al.* indicated (73) that the addition of 0.9% saponin, obtained from *Quillaja sp.*, to the diet of chicks depressed the serum cholesterol levels and the amount of deposition of cholesterol in the liver of animals maintained on a high cholesterol diet.

A similar finding in chickens was made by Clarkson and others (74) upon administration of gallogen (diethanolamine salt of monocamphoric acid ester of alpha,4-dimethylbenzyl alcohol).

Feinberg and his associates (75) were able to decrease the serum cholesterol and lipoprotein levels in dogs by the feeding of ethionine. Removal of the ethionine from the diet led to a prompt restoration of these serum lipids to pretreatment levels.

Coleman and Baumann (76) observed an increased excretion of sterols in rats following the administration of high levels of fiber in the diet but made no comment about the serum cholesterol levels of the animals. Walker and Arvidsson suspected (77) that the high fiber content of the Bantu diet accounted for their low serum cholesterol levels.

Kobernick (78) showed that exercise decreased the severity of the atherosclerotic process in rabbits. Over a 90-day period, 36 rabbits each received a total of 24.25 Gm. of cholesterol in the diet. The animals that exercised ten minutes daily on a treadmill had atherosclerosis rated as 2+ by Kobernick's grading system. The sedentary animals rated 4+ lesions.

Landsing (79) found that crystalline elastase (a pancreatic enzyme) lessened the severity of atheromatous lesions when given orally to cholesterol-fed rabbits. Tennent and others (80) obtained contrary results with this material in chickens. Mandl (81) has produced this material by a bacterial fermentation process. This enzyme has not yet been studied in humans but *in vitro* reports indicate that it acts by breaking down elastin, which has been found in atherosclerotic lesions.

Hormonal Therapy of Atherosclerosis

As far back as 1907, shortly after the introduction of reproducible methods for the production of atherosclerosis in experimental animals, Murata and Kataoka (82) discovered that the atherosclerotic process was more serious in castrated animals than in normal animals used as controls. Shapiro (83) reported in 1927 that thyroidectomy facilitated and accelerated the development of cholesterol-induced atherosclerosis in animals. Liebig (84) used iodine preparations to inhibit the development of experimental atherosclerosis in 1931.

Recent physicochemical studies of blood lipids have radically altered previously held concepts of lipid metabolism and modified theories concerning the activity of cellular elements of ground substance and their influence on lipid transport and metabolism. Investigations of endocrine mechanisms with respect to the atherosclerotic

disease state have been performed with the majority of the naturally occurring and synthetically prepared hormonal substances. An analysis of the information obtained from these researches appears to further implicate the interaction of many body mechanisms in the pathogenesis of atherosclerosis.

Thyroid.—Gould (85) commented that hypercholesterolemia resulting from hypothyroidism or myxedema is at present without explanation but is not, in his opinion, due to an increased rate of cholesterol biosynthesis in the liver.

Oliver and Boyd (86) have shown that both thyroid and estrogenic hormones significantly lower plasma cholesterol, cholesterol-phospholipid ratios, and the level of beta lipoprotein in the serum. These authors admit that the therapeutic value of reducing the level of circulating lipids in atherosclerosis has neither been confirmed nor refuted and, therefore, this approach to the treatment of the condition should be considered with caution. Emphasis is placed on the misleading concepts which can result from projection of experimental evidence from animal studies into the sphere of human conditions.

When the use of thyroid hormones or thyroid-like substances are contemplated for the lowering of serum cholesterol levels, their effects of increasing basal metabolic rate (BMR) and accelerating cardiac rates must be considered. These alterations may prove detrimental to euthyroid patients (87). Ultracentrifuge determinations indicate the ability of thyroxin to reduce concentrations of low-density lipoproteins in serum (88, 89). An increase in BMR and cardiac rate is also contraindicated in patients with an impaired myocardial blood supply resulting from atherosclerosis. These alterations might produce additional ischemia and aggravate the anginal syndrome.

Numerous analogs of the thyroxin molecule have been synthesized in the hope that a derivative could be found which would selectively lower elevated serum cholesterol levels without causing the undesirable cardiac and metabolic effects of thyroid hormone.

Gross and Pitt-Rivers (90) first isolated a thyroactive iodinated derivative—3,5,3′-triiodo-l-thyronine—which can result from a partial deiodination of thyroxin. Diiodo- and monoiodothyronine isomers have also been identified. If the alanine side chain of the diphenyl ether nucleus is modified by oxidative deamination or oxidative decarboxylation, additional interesting compounds are produced. The

oxidative deamination of thyroxin (91) yields tetraiodopyruvic acid, which can be decarboxylated to tetraiodothyroacetic acid or "tetrac." A similar process which triiodothyronine produces triiodothyroacetic acid or "triac" (92). Halogenated compounds such as tetrabromothyroxine (93) and tribromothyronine (94) have also been shown to have thyroxin-like activity in man. In myxedematous patients, "triac" (95) and "tetrac" (96) reduced the level of plasma cholesterol without increasing the BMR or cardiac rate. In euthyroid hypercholesterolemic men with proven coronary disease, both triiodothyronine (97) and "triac" (98) produced similar cholesterol lowering.

In spite of these initially encouraging results, clinical observations indicate that these substances are unsuitable for long-term therapy of hypercholesterolemic conditions. Analogs suitable for this use, devoid of intrinsic thyroid hormone activity, and to which tolerance will not develop, remain to be discovered.

Sex Hormones.—The role of estrogens in the atherosclerotic process has been a source of contention for many years. Numerous clinical and epidemiological surveys have demonstrated an apparent resistence of pre-menopausal women to coronary heart disease. This enigma became more intense when investigations revealed an apparent disappearance of this "immunity" after the menopause (1).

Four studies on humans have appeared relevant to the effects of estrogenic substances in the atherosclerotic condition. One of these reports (99) revealed that young ovarectomized women examined at autopsy several years after the ovarectomy exhibited a significant loss of the "immunity" to coronary atherogenesis normally associated with intact females of corresponding age. A separate study (100) showed that elderly males treated with estrogens at a high dosage level, for the control of prostatic carcinoma, had significantly less incidence or severity of atherosclerosis than untreated patients of the same age. In this study, it was also shown that women with mammary carcinoma, and presumably hyperestrogenic, evidenced less incidence of atherosclerosis than undiseased women of comparable age. Men and women with myocardial infarctions were found to secrete less biologically active estrogens and 17-ketosteroids than individuals unafflicted with this condition (101). Another observation (102) revealed that eunuchs had higher alpha and lower beta lipoprotein and cholesterol

levels and correspondingly less incidence of coronary atherosclerotic involvement than non-castrate men in similar age groups.

These changes might be attributable to some specific antiatherogenic effect of estrogens, but this possibility remains to be verified by further research. The action of estrogens in modifying blood lipid components has been shown to hold true for the synthetic preparations as well as the naturally occurring female sex hormones. Ethyinyl estradiol and PREMARIN (Ayerst) are probably the most widely used preparations among the estrogens for the treatment of hypercholesterolemic-atherosclerotic patients. Marmorsten *et al.* (10) reported that doses of ethinyl estradiol of 10 mcg./day had no effect on cholesterol/phospholipid ratios but lowered the serum cholesterol level in treated males. The more elevated the pretreatment serum cholesterol level, the greater was the lowering effect produced by estrogen treatment. At this 10 mcg. dose, no feminization was apparent. In the majority of cases, it has been impossible to dissociate the cholesterol-lowering action of estrogenic substances from their feminizing action, thus making the general use of these agents therapeutically in atherosclerosis impractical. A loss of sexual potency, gynecomastia, restlessness, and depression are associated with the use of this hormone in males.

High hopes were held for a synthetic estrogen analog (MANVENE, Searle) (103) based on the slight estrogenic activity it showed in the mouse and the high antiatherogenic effect seen in the chick. However, when clinical trials were undertaken, the low estrogenic activity seen in the laboratory was absent and the high incidence of feminizing effects in the male patients being treated in the study necessitated the termination of its use. The lipid lowering effects of this compound were not comparable to those obtained in the companion group treated with Premarin during this period.

Investigations of the male sex hormones have indicated that these substances have adverse effects and serve only to worsen the atherosclerotic process. Both Furman (104) and Russ (105) have reported deleterious effects on serum lipids from the administration of the male sex hormones. The availability of a 17-keto-steroid (NILEVAR, Searle), a compound showing a wide separation of androgenic and anabolic activities, prompted an examination of the action of a substance with this structure on lipid patterns of the serum. The results (106) showed that, while a true androgen (methyltestosterone)

profoundly elevated serum cholesterol levels and the estrogens produced an opposite effect, Nilevar caused great rises in beta lipoproteins but no significant effects on the serum cholesterol level.

Adrenal Hormones.—The role of adrenal hormones in lipid metabolism has been suggested by observations of Cushing's syndrome and Addison's disease. Recent experimental studies on bilaterally adrenalectomized dogs maintained on desoxycorticosterone acetate revealed a marked decrease in plasma cholesterol and phospholipid (107). Substitution of cortisone resulted in higher levels of both cholesterol and phospholipid in the plasma. Elevation of plasma-free cholesterol, without a corresponding increase in the esterified fraction, was observed by Wang and others (108) after the administration of cortisone, prednisone, and hydrocortisone to rabbits. This may indicate that a metabolic block in cholesterol esterification is part of the action of these steroids. Corticosteroid administration also resulted in an increase in neutral fat concentration in the plasma, due perhaps to impairment of fatty acid esterification. Despite the extreme elevations of all lipid fractions of the serum, adrenal hormone-treated animals exhibited less severe atherosclerosis than untreated controls. The suggested explanation of this finding was a decrease in vascular tissue permeability by the hormones (109).

It was shown that hyaluronidase caused the development of extensive atheromatous lesions in experimental animals, apparently from an increased permeability of the vascular tissues. This action could be counteracted by the administration of cortisone. These findings seem to support the concept that factors which modify the ground substance of the vascular wall are important in the deposition of lipids in these areas.

Dury (13) proposed that cortisone acts in the sulfate fixation portion of mucopolysaccharide synthesis and the consequent change it causes in lipid processes results in an accumulation of neutral fat and high S_f lipoproteins.

At the moment, no detailed human studies on the significance of cortical steroids in human atherosclerosis are available.

Many proprietary products having hormonal activity are presently available, but only those specifically discussed herein or presently employed therapeutically in hypercholesterolemia will be listed in TABLE III.

TABLE III

HORMONAL AGENTS

Product (Manufacturer)	*Active Ingredient and Content*
Thyroid	
CYTOMEL (SKF)	Triiodothyronine 5 and 25 mcg./tablet
PROLOID (Warner-Chilcott)	Thyroglobulin ¼ to 5 gr./tablet
SYNTHROID (Travenol)	Sodium-1-thyroxine 0.05, 0.1, 0.2 mg./tablet
THYROID U. S. P.	Powdered thyroid 0.1 to 5 gr./tablet
Estrogens	
ESTINYL (Schering)	Ethinyl estradiol 50 mcg./tablet
THEELIN (Parke-Davis)	Ketohydroxyestratriene 10,000 I. U./mg. 0.24 mg./capsule
PREMARIN (Ayerst)	Conjugated estrogenic substance 1.25 and 0.3 mg./tablet

Anticoagulant and Fibrinolytic Agents

In 1841, Rokitansky (110) in Vienna conceived the idea that deposits of material observed in the vascular wall at autopsy were derived primarily from fibrin and endogenous products of the blood mass rather than from an arterial exudate as proposed by other researchers.

Duguid (111) became interested in this theory of the genesis of atherosclerosis which had remained dormant and neglected for so many years. He restated the theory to the effect that an increase in fibrous tissue subsequent to thrombus formation caused a thickening of the intima and a decrease in the size of the arterial lumen. Astrup (112) studied the dynamic balance between fibrin formation and fibrinolysis and formulated an additional concept of the patho-

genesis of atherosclerosis, confirming and extending the Duguid theory.

Recent evidence tends to implicate fibrosis in both the atherosclerotic and the arteriosclerotic processes since Roth (113) has shown that the formation of the fibrin clot is substantially accelerated by an excess of fatty substances in the circulating blood. This reaction upsets the dynamic balance between fibrin formation and fibrinolysis; if fibrin is formed at a more rapid rate than it is destroyed, accumulations of this material occur in the vessels. This plays an important part in the complex activities of the vessel wall and eventually results in the formation of a necrotic area.

Based on these findings, several therapeutic approaches become evident. One approach is prevention of the formation of the fibrin clot by the prophylactic use of anticoagulants or, if the situation has progressed beyond this stage, fibrinolytic agents might possibly be employed to dissolve the fibrin formation. The other approach is the possibility of modifying circulating fatty substances by the action of lipemia-clearing agents. A number of reports indicate that anticoagulants in doses which do not produce an anticoagulant effect in the body are capable of producing a lipemic-clearing effect on the blood (1).

Anticoagulants.—Heparin had long been employed as an anticoagulant agent when Hahn (114) first observed its lipid-clearing action in 1943. Anderson and Fawcett (115) attributed the lipid-clearing action of heparin to the formation of a surface-active phospholipid complex. Further evidence indicated that heparin was involved in a physiological manner with lipid metabolism and that this mechanism was abnormal in atherosclerotic persons (1). The beneficial effects of heparin in atherosclerotic and hypercholesterolemic conditions remains the subject of considerable debate. Shaftel (116) showed that sublingual heparin was devoid of anticoagulant activity but useful as a serum lipid-clearing agent. The results of a 16-year study of patients with myocardial infarction, recently published by Conrad and Rothermich (117), show that anticoagulant therapy reduced the morbidity of the treated patients to one-third that of the untreated control group. The relationship of coronary artery pathology and abnormal lipid levels of the blood is confirmed by many reports in the literature.

Herbert (118) reported that different types of anticoagulants produced widely diversified effects on serum cholesterol levels of atherosclerotic patients. He claimed that no beneficial changes occurred as a result of heparin administration. SINTROM (Geigy) and TROMEXAN (Geigy) elevated both cholesterol and total lipid concentrations of the serum, but produced no significant alterations of beta lipoproteins during a 10-week treatment period.

It is understandable that the prolonged use of anticoagulant agents raises a question of advisability in the minds of many clinicians. The doses employed therapeutically for the lowering of blood lipids do not generally produce sustained increases in the clotting time of blood, but this is an individual matter which must be controlled and checked periodically in each patient.

Many compounds have been studied which possess little or no anticoagulant activity but are highly antilipemic in nature. Laminarin sulfate was reported by Mookerja and Hawkins (119) to be more active as an antilipemic agent, but to possess only one-third the anticoagulant potency of heparin. This material was obtained from *Laminaria digitata.*

Flokstra and Coleman (120) reported on studies of polyethylenesulfonate. In rabbits, this compound had twice the antilipemic action of heparin and was only one-half as active as an anticoagulant. The ammonium salt of polyethylenesulfonate was more effective than the sodium salt when administered orally to experimental animals and humans.

It appears that the antihyperlipemic and anticoagulant properties of substances similar to heparin are independent of one another.

Fibrinolytic Agents.—At the present time, the value of fibrinolytic agents in the treatment of atherosclerosis is unclear. Neff (121) summarized the current status of these agents in disease states. Weiner (122) recently demonstrated that parenterally administered nicotinic acid induced fibrinolytic activity in human subjects. This phenomenon did not occur *in vitro* or in other species but, at the moment, the reasons for this lack of activity remain obscure.

TABLE IV lists some of the anticoagulant agents available for use in hypercholesterolemic and atherosclerotic conditions.

TABLE IV

ANTICOAGULANT AGENTS

Product	*(Manufacturer)*	*Active Ingredient Content*
Parenteral		
HEPARIN U. S. P.		5000 U. S. P. units Heparin sodium/cc.
Oral		
CLARIN	(Leeming)	1500 I. U. Heparin potassium/ tablet
LIQUAMIN	(Organon)	3 mg. Phenprocoumon/ tablet

Agents Which Lower Blood Pressure

Some time ago, Page (123) proposed a "filtration theory" of atherogenesis. The important consideration in this hypothesis was the effect of increased lateral pressure on filtration through the vascular wall. Under normal circumstances, blood lipids were considered to filter through the vascular wall at a rate compatible with other metabolic processes of the body. Increases in the lateral pressure on the vascular wall modified this filtration rate and caused the blood lipids to accumulate in the wall of the vessel faster than they could be filtered through to the lymphatic ducts. This alteration, together with other factors, was considered responsible to a large extent for the atherogenic process. Schroeder (10) confirmed this concept and cited additional evidence in support of the hypertension-atherosclerosis relationship.

It is interesting to note that a localized pyridoxine deficiency (mentioned previously) is considered to act in initiating the atherosclerotic lesion formation and the production of a hypertensive state (124). It should be mentioned, however, that a generalized pyridoxine deficiency is accompanied by low blood pressure. Some common denominators of hypertension and atherosclerosis are discussed by Schroeder (10).

With respect to the value of the reduction of elevated blood pressure as a means of combating the atherosclerotic disease progress, a number of investigators have reported favorable results from the use

of antihypertensive drugs in atherosclerotic situations in both man and animals. Turner (124) cautioned those using blood pressure lowering agents against the abrupt change in blood pressure which these agents in large doses frequently cause. He suggested that gradual diminution of the blood pressure was the most suitable method of therapy to avoid adverse reactions in the patient.

In 1953, a report by Schroeder (125) mentioned that hypertensive patients being treated with a combination of hydralazine and hexamethonium had ". . . a tendency for the serum cholesterol to decrease." Since serum cholesterol levels are generally accepted as an indicator of atherosclerotic tendencies, it appeared that a therapeutic approach had been found which might cope simultaneously with both horns of this pathological dilemma.

Orvis and others (126) explored the coincident changes in serum cholesterol levels of hypertensive patients when treated with pentolinium, mecamylamine, and chlorisondamine. Their results showed that the patients treated with pentolinium had a decrease in blood pressure as might be expected but also experienced a decrease in the serum cholesterol level to an average of 57.8 mg.% less than their mean pretreatment level. In other hypertensive individuals, mecamylamine and chlorisondamine produced a 26% reduction from serum cholesterol pretreatment levels. In all three cases, it was observed that the administration of the drug produced greater reductions of blood cholesterol levels in hypercholesterolemic patients than the reductions observed in normal individuals.

Hollister (127) found that chlorpromazine (THORAZINE, S. K. F.) reduced the serum cholesterol levels in a group of psychiatric patients to whom it was being administered primarily for its psychotherapeutic effect. In this same report, evidence is presented that chlorpromazine produced a rapid fall of all elevated blood lipid fractions in two patients with essential hyperlipemia. Essential hyperlipemia is a rare condition for, in 1954, only 48 cases were recorded in the literature (128). Following the lead of this initial study, Hollister (129) investigated chlorpromazine more thoroughly and included in this study the adrenergic blocking agents DIBENZYLINE (S. K. F.), HYDERGINE (Sandoz), and REGITINE (Ciba). In his experimental design, Hollister chose to consider as a significant change a reduction of 25 per cent from the mean control value before treatment. His experimental group consisted of 13 patients. While

the results of his studies tend to indicate that these agents have the ability to reduce elevated serum cholesterol levels, the data obtained from this small sample appear insufficient to permit a conclusive decision. Hollister explained that his purpose in these investigations was to evaluate the possibility that adrenergic blockade might have an effect in the neurohumoral mechanisms associated with the control of lipid metabolism. The agents tested all shared the common property of being adrenergic blocking substances.

Somoza (130) found that reserpine decreased elevated serum cholesterol levels and the severity of atherosclerotic lesions in rabbits. Similar findings were reported by Smith and Rossi (131) for both reserpine and mecamylamine in rats. Krag and his co-workers (132) observed no alterations of serum cholesterol or serum lipoproteins resulting from the administration of resperpine in humans over a one-year period.

Summary

Great advances have been made in our knowledge of atherosclerosis but great gaps still exist. Disagreement persists over the exact influence of cholesterol in the atherosclerotic process. The relationship of atherosclerosis and hypertension is not clearly established, and additional etiological factors remain to be identified.

The investigations of researchers in collateral fields appear to revert to alterations of cholesterol metabolism as the important precursory factor in this disease process.

An examination of the agents which have been employed for the prevention or the treatment of atherosclerosis reveals that the majority produce hypocholesterolemia. The sharing of this property by chemically and pharmacologically unrelated substances seems an unusual phenomenon.

It is possible that, in time, an understanding of the pathological mechanisms responsible for atherosclerosis will be fully understood. In the interim, the apparent approaches to the treatment of atherosclerosis are primarily those which are described in this review.

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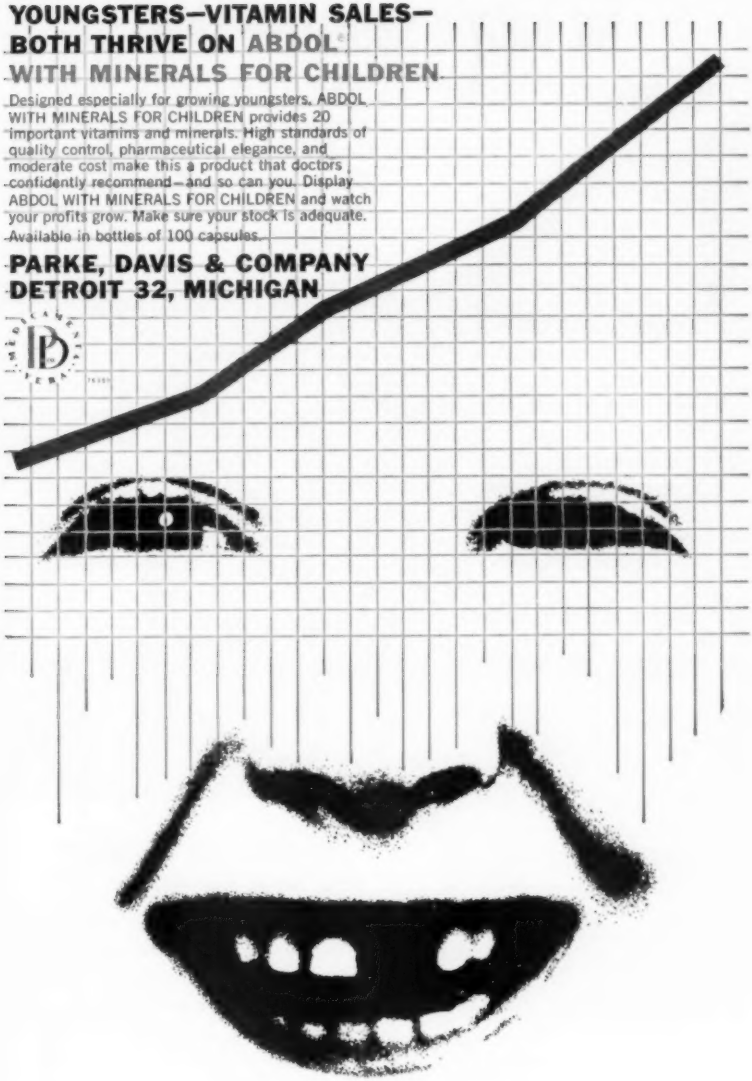

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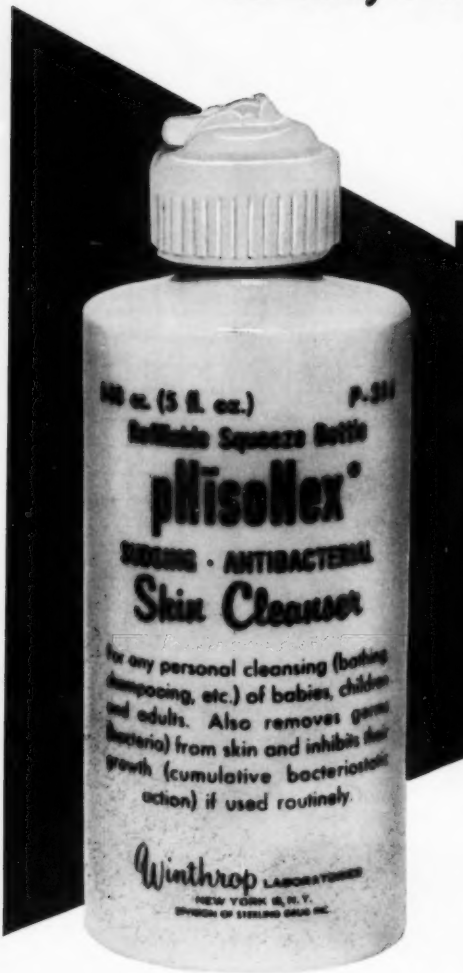

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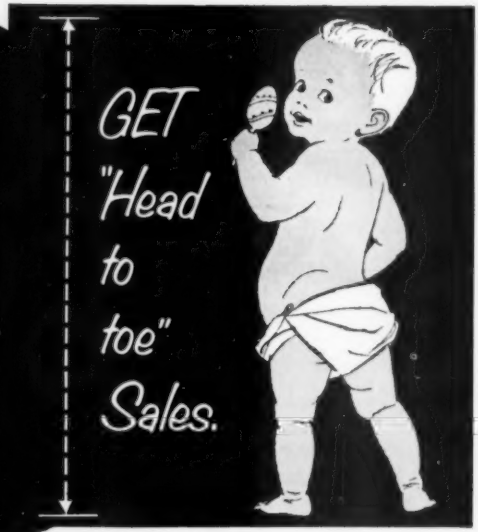

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